VOL. 33 JANUARY, 1906 NO. 1

THE
Journal
OF
Nervous and Mental Disease

Original Articles

A STUDY OF TWO UNUSUAL BRAIN TUMORS; ONE A MULTIPLE CYLINDROMA OF THE BASE OF THE BRAIN, THE OTHER A NEURO-EPITHELIOMA OF THE CHOROID PLEXUS OF THE FOURTH VENTRICLE.*

BY HERMON C. GORDINIER, A.M., M.D.,
OF TROY, N. Y.,
PROFESSOR OF PHYSIOLOGY AND ANATOMY OF THE NERVOUS SYSTEM IN THE ALBANY MEDICAL COLLEGE; PHYSICIAN TO THE SAMARITAN HOSPITAL;

AND H. W. CAREY, A.B., M.D.,
OF TROY, N. Y.,
INSTRUCTOR IN SURGICAL PATHOLOGY, THE ALBANY MEDICAL COLLEGE, AND PATHOLOGIST TO THE SAMARITAN HOSPITAL.

Case I.—Multiple cylindroma of the base of the brain, involving the second, third, fourth and eighth cranial nerves, and producing symptoms closely simulating a tumor of the quadrigeminal bodies.

December 1, 1903. Saw in consultation Mr. C., aged forty-nine years, married, laborer by occupation. His chief complaints were severe continuous headache, dizziness, difficulty in walking, deafness, and failing vision.

Family History. Father died of heart disease, mother of cholera. He had lost nine children, six in infancy, two of smallpox, and one was accidentally killed. No insanity or nervous diseases in family. Previous history negative.

Present illness began in the early part of June, 1903, with dizziness and severe dull headache, confined chiefly to the right side. A short time after the patient noticed peculiar hollow sounds and noises in each ear as if steam were escaping or gongs were ringing. In July, 1903, discovered that he was becoming deaf in the right ear. Three weeks later hearing

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*Read at the meeting of the American Neurological Association, June 1, 2 and 3, 1905.

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was lost in the left ear. In the early autumn his gait became unsteady and he swayed from side to side like a drunken man.

Examination. The patient is a tall, slightly built man with flabby musculature and considerably emaciated. The temporal and radial arteries are thickened. The apex beat is slightly displaced downward and outward and the aortic second sound is accentuated. There are no adventitious sounds. The cardiac dulness is entirely effaced and the upper line of liver dulness diminished by a vesiculo-tympanitic note. The lungs are normal except for a moderate degree of emphysema. The urine is negative.

Nervous System. Cranial Nerves. The pupils are unequally dilated, the left being the larger. They respond very sluggishly to light and accommodation. The eyeballs are held in a position of moderate divergence, the only movement of the globes permissible being in a slightly upward direction. Ptosis is present on both sides, being most marked on the left. The patient is able to distinguish and name objects accurately, recognizes colors, but is unable to read moderately coarse print. Optic neuritis exists, more accentuated in the left eye.

The facial muscles present no tremor, atrophy or asymmetrical action. The tongue is protruded straight and is normal in size and appearance. The palatal and pharyngeal muscles functionate normally.

No anesthesia or analgesia of either side of face; no rigidity of neck muscles. Smell and taste are normal. The vocal bands move in a normal manner.

The patient is unable to hear either a loud ticking watch or a tuning fork, when held close to the ears. The bone conduction is greatly and equally diminished on each side. The left drum membrane was normal. The right auditory canal was so occluded by a plug of old wax that it was impossible to view the drum.

Reflexes. Patellar reflexes are lively; no patellar or ankle clonus. No Babinski sign. The Achilles tendon reflex is normal on each side; no Kernig sign. Tendon reflexes of the upper extremities absent, all superficial reflexes normal.

Sensation was very carefully tested and found normal.

There is no loss of stereognosis. No loss of muscular sense. Motor power normal, muscles wasted only from disuse.

The patient's gait is typically cerebellar in type, he is unable to walk without assistance and sways from side to side as he progresses, his feet being widely separated so as to broaden his base of support.

His memory is gradually failing both for past and recent events, his cerebration is slow. No aphasia exists.

The general symptoms in this case, i.e., severe headache, dizziness and double optic neuritis clearly pointed to an intracranial lesion, probably a new growth, while the order of appearance of the focal symptoms, i.e., almost complete deafness, preceded by bilateral auditory hallucinations of peculiar sounds, as if steam was escaping or gongs ringing and followed by a typical cerebellar gait, and almost complete ophthalmoplegia externa and interna, seemed in our judgment to place the primary position of the lesion in the region of the dorsal quadrigeminal bodies. The central gray matter situated about the aqueduct of Sylvius was thought to have become involved

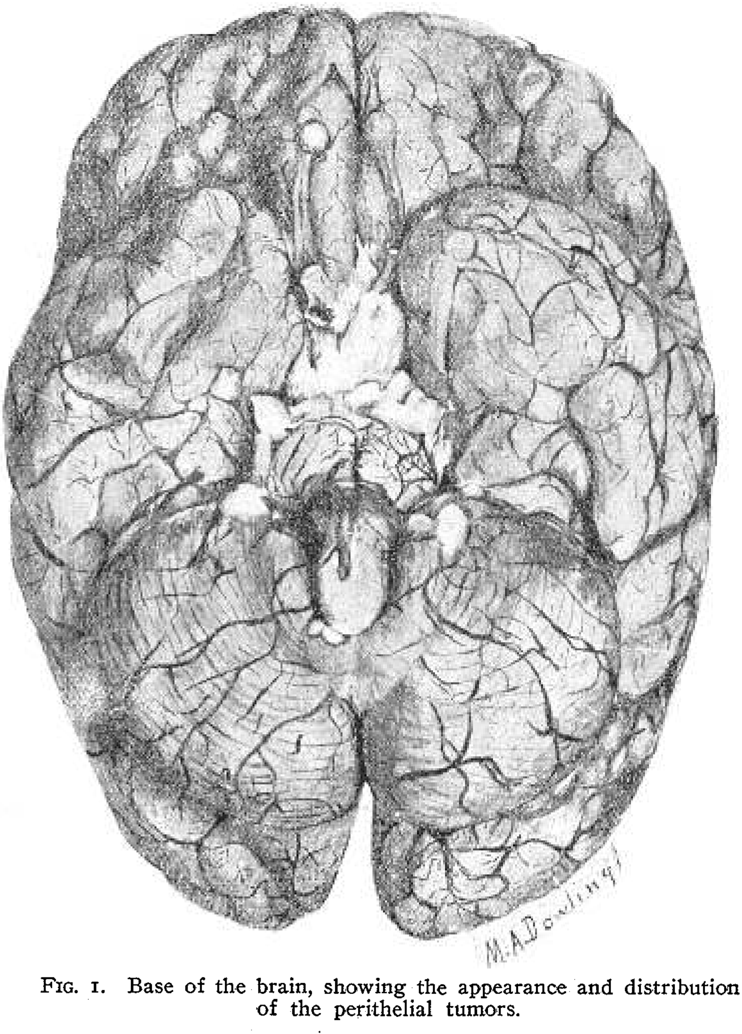


Fig. 1. Base of the brain, showing the appearance and distribution of the perithelial tumors.

secondarily, by a ventral extension of the growth, thus destroying the nuclei of origin of the third and fourth cranial nerves and causing the ophthalmoplegia.

The auditory auræ and deafness and the incoordination seemed equally well explained by this localization of the lesion. The former being due to an irritation with destruction of the central auditory tracts, "lateral fillets," the latter either to compression of the central part of the median worm or the ventral cerebellar peduncles. The patient was placed on large doses of potassium iodide together with mercurial inunctions with the hope that the lesion might be gummatous in nature. He was seen again on January 15, 1904, after six weeks of continuous mixed treatment. He was confined to bed unimproved, in fact all symptoms were much worse. The incoördination was so extreme that he was unable to stand or to take a step. He died two weeks later of exhaustion.

Autpsy—Dr. Gordinier. No abnormality in the cranial bones. The membranes were normal. Sinuses and surface veins not obstructed. No increase of cerebro-spinal fluid. The brain was hardened in toto and later sectioned. On the base of the brain multiple tumor formation was noted, the tumors were distributed as follows. One tumor 0.5 cm. in diameter on each olfactory bulb, one tumor 3.0 x 2.5 cm. in the interpeduncular space, inclosing the optic nerves, optic commissure and third and fourth nerves; four small tumors on the internal surface of the temporo-sphenoidal lobe varying from 0.2-0.5 cm. in diameter, two tumors 0.5 cm. in diameter on the anterior surface of the pons, one tumor on the base of the right lobe of the cerebellum. At each cerebello-pontine angle exists one of these tumors encircling and compressing each auditory nerve close to its point of connection with the pons. Isolated tumor masses of the same material were also found infiltrating each auditory nerve at its exit from the internal auditory meatus. On section, one tumor 0.4 cm. in diameter on the internal aspect of the left frontal lobe and two tumors symmetrically placed in the angle between the caudate nuclei and corpus callosum in the lateral ventricles, 0.5-0.2 cm. in diameter. From the above it is seen that the tumors presented no symmetry in arrangement. The size varied within wide limits, the smaller tumors representing more recent growths, the largest one in the interpeduncular space being in all probability the first one to develop. Macroscopically it is seen that the smaller tumors are attached to the visceral layer of the pia mater and are removed with it when it is stripped off. The larger tumors do not show so distinctly this attachment to the pia mater and are frequently found infiltrating the cortex. The tumors were grayish in color and had the consistency and appearance of soft cartilage.

Microscopically the tumors appear to be composed of aggregations of minute globules of opalescent hyalin-like refractive material. So far as can be seen there is no stroma whatever.

Teased preparations from the fresh tumor showed mostly globules, less often strings of homogeneous hyaline-like material in the center of which are cells. The larger masses are made up of aggregations of these globules. The basement substance occasionally shows striations or fibrillæ. Several of the tumors were excised and some were prepared according to the Weigert-Pal method to determine the extent of the degenerative changes in the basal nerves and cortex, others were imbedded in paraffin and stained in a variety of ways for histological study.

Microscopically the basement substance greatly exceeds the cellular elements. In the small growths the pia mater is extending over the growths at the margins and presents here a fairly normal appearance. The endothelial cells are, however, slightly swollen; over the central or basal portion no trace of the pia is seen. The portions of the tumors bordering the pia show the greatest amount of basement substance, cellular elements are rarely seen.

The cells are most numerous in the portions bordering the cortex. They are placed in cavities of the basement substance either singly or in groups, and are surrounded by a wide meshed reticular substance. No definite boundary divides one cell from another, they form rather irregular masses of multinucleated protoplasm often vacuolated or containing droplets of fluid.

The nuclei are of variable size, some being as small as a red blood corpuscle, others several times larger, the smaller ones taking a deep hematoxylin stain, the larger ones showing a more reticulated structure. The matrix with the cells have the appearance of syncytium. The presence of droplets in the cells, makes it probable that the basement substance is derived from them. At some distance from the syncytial masses the basement substance becomes denser and has a homogeneous appearance like that of hyaline cartilage. To determine the character of the basement substance, sections were stained with thionin and with polychrome methylene blue. The looser portions bordering the cells take a distinct reddish tint characteristic of mucus, the denser portions are bluish red like the hyalin of cartilage.

With the iodine test no glycogen could be found in the cells. In some portions of the tumors the appearance of the single cells in lacunæ, surrounded by hyaline basement substance bears a close resemblance to hyaline cartilage and has been so interpreted by Meckel, Boettcher and others, but in these tumors the growth is essentially a proliferation of perithelial cells which secrete the basement substance. While endothelial or perithelial cells are primarily of mesoblastic origin and closely related to connective tissue, they represent a differentiated form, and not true connective tissue. There is no connective tissue in the tumor, from which this hyaline could be formed, so in spite of its close resemblance to cartilage we do not look upon it as such.

The method of growth is seen clearly at the periphery of the tumor in the cortex. The syncytial masses here are in the form of long narrow strings and frequently in the center of these there is a double row of flat endothelial cells, often with a lumen containing red blood corpuscles. The tumor cells are on either side of these capillaries and even at this early stage and while actively growing, show vacuoles, and droplets of fluid, and are surrounded by mucus. The basement substance here is probably therefore a secretion from the tumor cells.

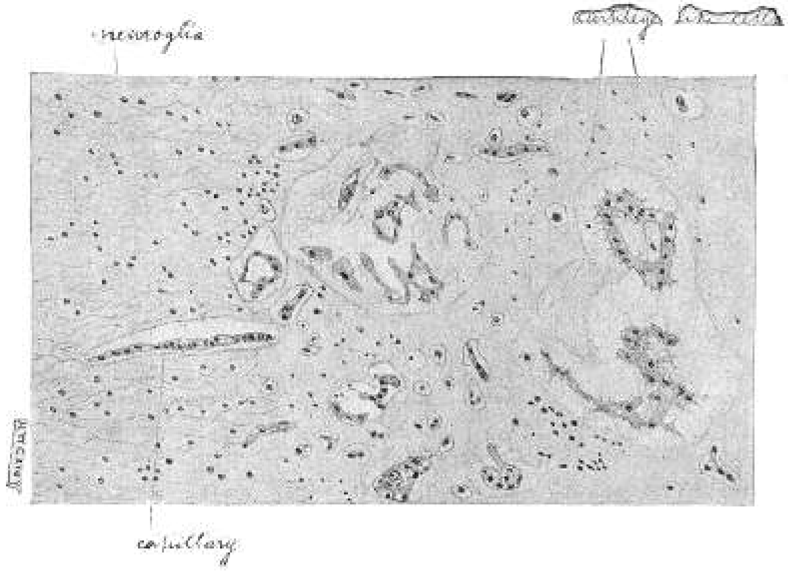


Fig. 2. Case I. Perithelioma, showing the mode of extension by capillary growth into the cerebral cortex.

As the perivascular cells proliferate and throw out their secretion, the capillary is compressed and finally obliterated. Fully developed blood vessels are rarely seen and when present do not form a part of the tumor, but are cerebral or pial vessels.

The tumor therefore is primarily a perithelioma, springing from the perithelial cells in the walls of the blood capillaries and rapidly undergoing hyaline metamorphosis. To such tumors of endothelial origin with extensive hyaline changes and the formation of hyaline balls and cylinders Bilroth has given the name of cylindroma. This tumor then is a hæmangio-perithelioma cylindromatosum.

Sections of the growth in the interpeduncular space stained by the Weigert-Pal method show that the tumor has invaded the optic commissure, the optic, third and fourth nerves and has caused extensive degeneration in them as well as in the basal cortex.

In seeking the point of origin of these tumors it may be said that in none of the sections could any connection between the tumor and the pia be traced. At the margins of the tumors, the pia shows only a slight reactive swelling, and over the central portions it has undergone atrophy probably from pressure. The growths are located between the pia mater and the cerebral cortex and in origin are independent of both.

Inasmuch as they cannot be traced to any of the fixed tissue elements they probably originated from cells included in the brain in its early development.

As to the nature of the cells inclosed, their immediate development into capillaries suggests that they were destined to form such structures in the ordinary course of their development, that is vaso-formative cells. The multiplicity of the tumors favors this mode of origin, for the numerous growths are not the result of metastases, but are distinct from each other in their development. Their location on the base of the brain near the line of closure of the cerebral vesicle, and the growth of the cells in the form of syncytium, is also in favor of their development from inclosed germinal cells.

The malignancy of the tumors is not marked, for although there is a tendency to invade the cortex as described in the optic chiasm, optic, third, fourth and auditory nerves, the invasive power is diminished by the lack of proper vascular supply.

Multiple endothelial tumors of the brain are not infrequent, but such an advanced grade of hyaline degeneration so far as can be determined, has not been hitherto described.

Multiple cylindroma of the spinal cord have been observed however by Glaser and by Ganguillet and in appearance closely resembles this tumor. A thorough search of the references on this point however is almost impossible on account of the varied nomenclature applied to this form of tumor.

In conclusion we beg to call your attention to the fact that the peculiar distribution of the tumors anatomically, produced a symptom-complex highly suggestive of, and by Nothnagel attributed to, a lesion of the quadrigeminal bodies.

Case II.—A Neuro-epithelioma of the choroid plexus of the *fourth ventricle, growing dorsally and producing symptoms characteristic of a tumor of the median lobe of the cerebellum.*

December 30, 1898. W. K., aged ten years, German. Father living and well. Mother died of some stomach trouble, probably cancer. Has had measles, varicella, mumps and pertussis. No history of any nervous disease or insanity in family. Never received an injury to his head.

Present illness began about November 1, 1898, with the symptoms of la grippe, and severe occipital headache. Later the headache became general. He tired easily, and would have frequent and very severe dizzy spells: In December he left school, because of the severe headache and his inability to remember his lessons. Soon after, his gait became so affected that in order to walk he would have to support himself by pushing forward a chair.

Present Condition. Pupils dilated, equal, and respond but slightly to light and accommodation. Excursion of eyeballs normal. Slight lateral nystagmus. Double optic neuritis. No hemianopsia. Hearing normal in left ear, but is reduced in the right, because of a chronic otitis media.

Examination of eyes by Dr. F. A. Smith; Right eye. V-20-50, pupil large, 9 m.m. in diameter; reacts to light and accommodation; media clear; disc swollen 3 D, outline not discernible; veins enlarged; arteries normal; field of vision slightly diminished on temporal side. Left eye, V-20-90; pupils large, 9 m.m in diameter, disc swollen 3 D; field of vision normal. The internal ocular muscles of both eyes are normal.

No facial asymmetry. Tongue protrudes straight. Sense of taste and smell normal. Vocal cords move normally. Patient sways to the right side when he stands or attempts to walk. This is very marked when he walks backward. Romberg's symptom not marked. Movements of upper extremities a little awkward, but otherwise normal. Sensation is everywhere normal.

Reflexes—Right patellar reflex slightly exaggerated. Left normal. No ankle-clonus. Superficial reflexes of both sides preserved and normal.

Heart, lungs and urine normal.

February 1, 1899. Patient's condition is very much worse. Headaches very severe. There is rigidity of the neck and upper part of the spine. Scalp is very tender, over occipital and parietal regions, and on percussion, there is distinct tympanitic note over both parietal bones. A few days ago, he had a dizzy spell, staggered forward, seemed dazed and said he could not see. During this attack the pupils became widely dilated, and there was an evanescent loss of consciousness. When he awakened, he was in a bewildered state and frequently asked where he was. He complains, also, that his feet are icy cold most of the time.

March 1, 1899. His breathing is irregular and labored. Has frequent attacks of hiccough and some difficulty in swallowing. Pulse is rapid and feeble. Died, March 7, 1899, at 7 a.m.

Autopsy at 8.30 p. m. Pupils equal and widely dilated. Eyeballs slightly divergent. Glabella to occipital protuberance, 35.5 c.m.; circumference at zygomatic processes, 58 c.m. Skull cap, over lower temporal regions is very thin. In a few places over the vertex, it is as thin as paper. Vessels of pia distended. Convolutions flattened. Dura thinned, not adherent and normal. There is a very great increase of the subarachnoid fluid and the lateral and third ventricles are distended. The nerves at the base are perfectly free, and normal in appearance. The oblongata is pushed forward. On section, through the median lobe of the cerebellum, a tumor was discovered irregularly quadrilateral in shape, measured 3.5 c.m. anteroposteriorly, and 2.75 c.m. transversely. This tumor

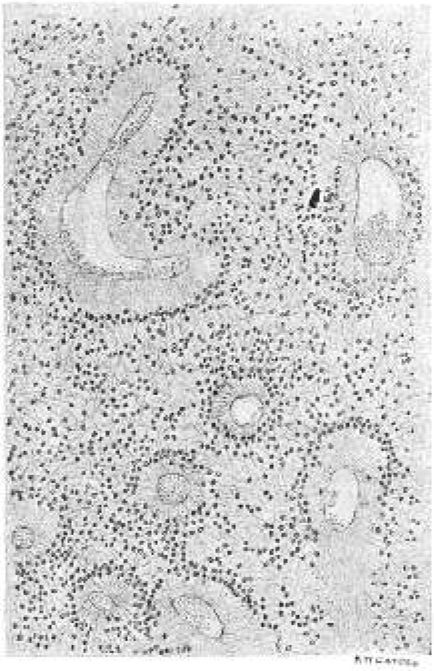


FIG. 3. Case II. Shows the rosette formation and neuroglia tissue between.

was very vascular and was located in the fourth ventricle, almost completely filling it. It took its origin from the choroid plexus. In its growth forward and upward, it pushed itself through the velum medullare posterior, compressed and grew into the inferior worm of the cerebellum. Upon examination of the tumor microscopically, under low magnification, three fairly distinct elements can be distinguished: tumor cells, fibers and blood vessels. A description of each element will be given first, then their relationship to one another.

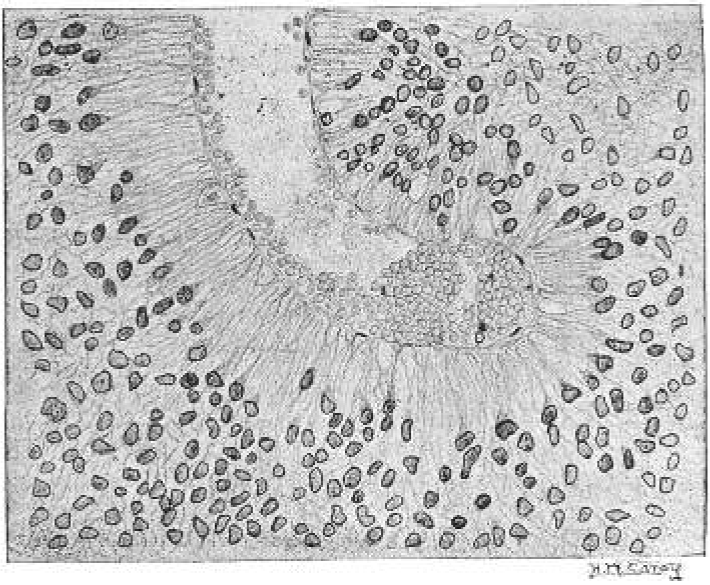
The tumor cells are of two kinds although there are many gradations between. One cell form (type A) is of small size with oval or round deeply staining nuclei and only a small rim of protoplasm around them. They closely resemble lymphocytes in size and appearance.

The second cell form (type B) closely resembles glia cells, they show a varied cell outline, a generous amount of protoplasm with numerous processes or fibrils extending outward, sometimes only from the poles, sometimes from the whole periphery. The fibrils when single are very thin and delicate, they often coalesce to form thicker cords. Most of the fibrils are attached to the cell body but some are free. They form a network in which the cells are placed. The blood vessels are numerous at the periphery of the tumor, their walls have undergone hyaline degeneration, in the central portions, the capillaries are very numerous and give a plexiform appearance to the tumor.

The tumor is attached to the median lobe of the cerebellum above, but the cerebellar tissue takes no part in the growth and appears compressed, but is otherwise normal.

The ependymal cells lining the inferior surface of the velum are normal in appearance, except where they approach the attachment of the tumor, here they are flattened and are reflected over the outer surface of the tumor for short distance and then merge gradually into the tumor cells of type A. At the periphery and near the base of the tumor, the cells are almost exclusively of type A. They often arrange themselves in groups of eight or ten cells with nuclei peripheral and protoplasm central, no lumen, however, is seen. Structures similar to these are seen in ependymitis granulosa. This portion of the growth is very cellular, few fibers are present. Toward the center the blood vessels become more numerous although smaller in size and are surrounded with a mantle of cells with a band of fibers, radially arranged, intervening. The cells are in several layers about the vessels with nuclei toward the periphery.

The fibers originate from these cells and extend inward toward the capillary, are closely placed and frequently unite before reaching the vessel wall. From the periphery, fibers also extend and form part of the general network of fibers. The central vessels with the radiating fibers and surrounding mantle of cells, form characteristic structures, which are termed rosettes. Between the rosettes, which form the main mass of the tumor, are cells of both types and all gradations between them. There are some areas which begin with a hyaline degeneration of the vessel wall, then hyaline masses are found in the spaces between the fibers immediately surrounding the blood vessel. Eventually the whole rosette undergoes hyaline degeneration.



Case 2. Muthmann. Ziegler's Beiträge, 1903, No. 34, p. 445.
FIG. 4. Case II. Rosette; high magnification.

Origin. From these facts we feel justified in assuming that this tumor sprang from the ependymal cells of the choroid plexus of the fourth ventricle. Whether the growth began primarily in the ependyma or in the blood vessels we can not determine, but the epithelial structures form the main mass of the tumor and are the essential element of its growth. The gradual change of the ependymal cells into glia cells we interpret as a metamorphosis into their embryonic form, a metaplasia.

This form of tumor has been named neuro-eptheliona by Flexner who first described a tumor of somewhat similar tructure to this one in 1891, which had its origin in the external nuclear layer of the retina. They have also been termed ependymal glioma, but as Flexner pointed out in his original communication, this is improper in that the growth originates from the epithelium and not from neuroglia.

Ependymal tumors are not common. Muthmann has collected and abstracted fourteen cases from the literature. Flexner has reported a second case which so closely resembles the one here described, that it requires no further mention.

More recently Mallory has described three ependymal tumors, one of which was located at the mid line of the coccyx and was about the size of an orange. Microscopically it looked much like a carcinoma, but between the cells were neuroglia fibers, and in the cell protoplasm were found the granules (Körnchen) described by Weigert as characteristic of ependymal cells.

Tumors of the oblongata owing to the close approximation of the motor and sensory tracts, and the nuclei and root fibers of the eight, ninth, tenth and twelfth pairs of cranial nerves, together with centers of respiration, circulation and those controlling the vasomotor nerves, create symptoms which are very characteristic, such as nerve deafness, paralysis with atrophy of the tongue, soft palate, muscle of pharynx, producing dysphagia, dysarthria, or paralysis of one or the other vocal cords. Of common occurrence are disturbed heart action , attacks of dyspnea, of Cheyne-Stokes breathing, and polyuria. These symptoms are frequently accompanied by bilateral or alternating paralysis of the extremities, with or without sensory disturbances or ataxia, and marked increase of the deep reflexes. Tumors of the fourth ventricle when compressing its floor are accompanied by very marked vasomotor, cardiac and respiratory changes together with other bulbar symptoms. Not infrequently sudden death ensues from the sudden compression of the node vital of Flourens. In this case none of the above mentioned symptoms were present, and the autopsy showed that the growth grew dorsally through the posterior medullary velum into the median lobe of the cerebellum, compressing and in part destroying it. It is remarkable, owing to the position and size of the tumor, that the important tracts and centers in the medulla were not early involved.

NOTE.—Neuroglia stains were not successful as the tumor had been left in the hardening fluid (Müller's) for a year or more.

LITERATURE.

Case. 1. Flexner. Johns Hopkins Hospital Bulletin, 1891, p. 115.

Case 2. Muthmann. Ziegler's Beiträge, 1903, No. 34, p. 445.

Case 3. Weigert. Festschrift zum 50 jährigen Jubilaum des arztlicher Vereins zum Frankfort, 1895.

Case 4. Mallory. Journal of Medical Research, Vol. VIII, June, 1902.